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Extraction of respiratory signals from the electrocardiogram and photoplethysmogram: technical and physiological determinants

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Abstract

Objective: Breathing rate (BR) can be estimated by extracting respiratory signals from the electrocardiogram (ECG) or photoplethysmogram (PPG). The extracted respiratory signals may be influenced by several technical and physiological factors. In this study, our aim was to determine how technical and physiological factors influence the quality of respiratory signals.

Approach: Using a variety of techniques 15 respiratory signals were extracted from the ECG, and 11 from PPG signals collected from 57 healthy subjects. The quality of each respiratory signal was assessed by calculating its correlation with a reference oral-nasal pressure respiratory signal using Pearson's correlation coefficient.

Main results: Relevant results informing device design and clinical application were obtained. The results informing device design were: (i) seven out of 11 respiratory signals were of higher quality when extracted from finger PPG compared to ear PPG; (ii) laboratory equipment did not provide higher quality of respiratory signals than a clinical monitor; (iii) the ECG provided higher quality respiratory signals than the PPG; (iv) during

downsampling of the ECG and PPG significant reductions in quality were first observed at sampling frequencies of <250 Hz and <16 Hz respectively. The results informing clinical application were: (i) frequency modulation-based respiratory signals were generally of lower quality in elderly subjects compared to young subjects; (ii) the qualities of 23 out of 26 respiratory signals were reduced at elevated BRs; (iii) there were no differences associated with gender.

Significance: Recommendations based on the results are provided regarding device designs for BR estimation, and clinical applications. The dataset and code used in this study are publicly available.

Keywords: respiratory modulation, biomedical signal processing, electrocardiography, photoplethysmography, respiration

(Some figures may appear in colour only in the online journal)

1. Introduction

Breathing rate (BR) is widely used for diagnosis and prognosis. On general hospital wards BR is usually measured by manually counting chest wall movements. This practice is time-consuming, inaccurate, and poorly carried out (Lovett *et al* 2005, Cretikos *et al* 2008). An alternative approach may be to estimate BR from electrocardiogram (ECG) or photoplethysmogram (PPG) signals, which are already routinely measured in a wide range of clinical contexts. A recent study in a young, healthy population showed that BR can be estimated from the ECG and PPG signals with a similar precision to Impedance Pneumography, the current clinical standard for electronic BR measurement (Charlton *et al* 2016a). These results were obtained from young, healthy volunteers at rest using high fidelity signal acquisition equipment, so it is not yet clear whether they can be generalised to clinical settings.

A fundamental step in estimation of BR from the ECG and PPG is the extraction of a respiratory signal: a signal dominated by respiration. Respiratory signals can be extracted from the ECG and PPG using either feature- or filter-based techniques, as illustrated in figure 1. The processes for extraction of respiratory signals are demonstrated in figure 2. In this figure extraction of respiratory signals is illustrated for each of the three idealised types of respiratory modulation of the ECG and PPG: baseline wander (BW), amplitude modulation (AM), and frequency modulation (FM) (Charlton *et al* 2016a). If the amplitude of the respiratory signal is too small compared to the underlying noise, then the signal may not be distinguishable from the noise, preventing the precise estimation of BR. Thus, any factors which reduce the amplitude of respiratory modulations may result in reduced respiratory signal quality, affecting the estimation of BR from these signals.

The aim of the study presented in this paper was to determine how the quality of respiratory signals is affected by technical and physiological factors which may be encountered in the clinical setting. Technical factors are those which are fixed during device design, such as the choice of either ECG or PPG as the signal from which respiratory signals are extracted. It is important to understand the influence of technical factors to optimise device design. In contrast, physiological factors cannot be controlled for. The influences of physiological factors, such as age, can inform decisions on whether or not particular BR algorithms are appropriate for use in particular clinical scenarios. Quality was measured using the correlation between an extracted respiratory signal and a reference respiratory signal (see figure 1).

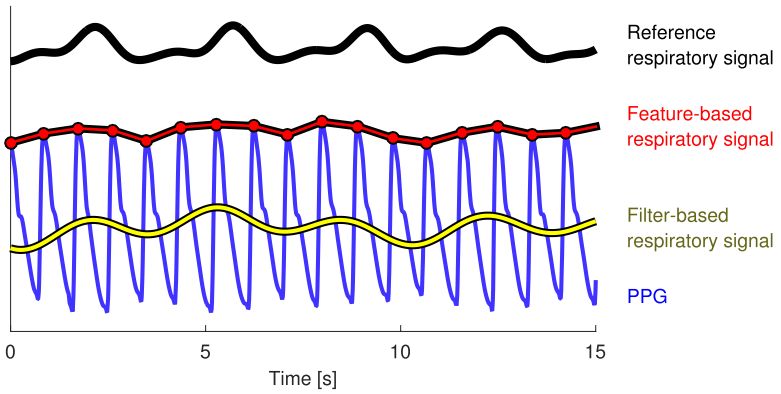

Figure 1. Extraction of respiratory signals using exemplary feature- and filter-based techniques. Respiratory signals have been extracted from the PPG using a feature-based technique in which pulse peak amplitudes are extracted, and a filter-based technique using the amplitude of the continuous wavelet transform. In this study the quality of extracted respiratory signals was assessed by calculating the correlation between each extracted respiratory signal and the reference respiratory signal. Adapted from Pimentel *et al* (2015).

The paper is structured as follows. Firstly, a review is presented of previous investigations into the influence of technical and physiological factors on respiratory signals of the ECG and PPG, and the subsequent performance of BR algorithms. Secondly, the methods are described for data collection, assessment of the quality of respiratory signals, and statistical analysis. Thirdly, the results are presented for each technical and physiological factor in turn. Finally, the impacts of these factors on device designs and on the use of BR algorithms in particular clinical scenarios are discussed. The dataset, respiratory signal extraction algorithms, and analysis code used in this study are publicly available at: http://peterhcharlton.github.io/RRest.

2. Review of previous work

The previous work relating to each of the factors assessed in this study is now reviewed.

2.1. Technical factors

PPG probes can be positioned at a range of anatomical sites, including the finger, ear, forearm, shoulder and forehead (Nilsson *et al* 2007). Of these, only finger and ear measurements are widely used in clinical practice. The quality of respiratory signals extracted from the PPG may differ at different sites because of the augmentation of the systolic portion due to arterial pressure wave reflections (Elgendi 2012), and the visco-elasticity of the arterial system (Alastruey *et al* 2011). Indeed, previous investigations have shown that the amplitude of BW is greater when the probe is positioned at the ear than the finger (Shelley *et al* 2006, Nilsson *et al* 2007). However, further investigation is required to verify this finding and determine the effect of measurement site on AM and FM signals. This may impact device designers' considerations of the site of PPG measurement for BR estimation.

The equipment used to acquire ECG and PPG signals may influence the quality of respiratory signals. This is of particular concern with the PPG, since clinical monitors commonly

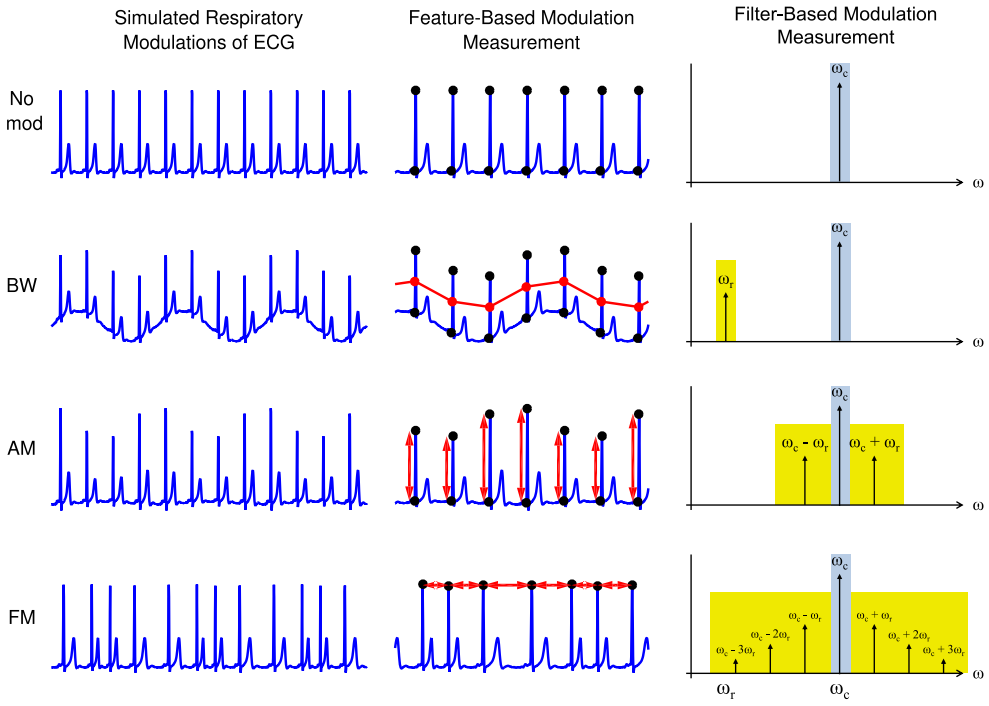

Figure 2. Processes for extraction of respiratory signals. On the left from top are shown simulated ECG signals with no modulation, baseline wander (BW), amplitude modulation (AM), and frequency modulation (FM). In the central column the Q- and R-waves have been identified (shown as dots), allowing feature-based modulation measurement of BW, AM and FM (shown in red). On the right are the corresponding frequency spectra of idealised signals at the cardiac frequency (ω_c) under the influence of each modulation. Filter-based modulation measurement consists of extracting signals dominated by the respiratory frequency. Note that only BW is manifested in the respiratory frequency (ω_r) band. Adapted from: Charlton *et al* (2016a) (CC BY 3.0), Charlton *et al* (2016b) (CC BY-NC 4.0), Pimentel *et al* (2015).

output a filtered version which has been optimised for display, which may differ from the measured signal (Feldman 2010). The processing procedures include auto-gain, auto-centre, and amplitude gain functions (Shelley 2007). These adaptive filters may function over a short time scale, comparable to that of breathing, therefore potentially affecting extracted respiratory signals. Indeed, a recent study reported that the AM signals extracted from PPG signals acquired from two clinical monitors were not interchangeable (Høiseth *et al* 2015). Since monitors' filtering characteristics are not usually published (Feldman 2010), it is not clear how extracted respiratory signals are affected by this process. If high-fidelity laboratory equipment results in higher quality respiratory signals than a clinical monitor, then device designers may need to consider modifying the hardware in devices in order to extract high quality respiratory signals prior to filtering.

The type of input signal, ECG or PPG, may impact the quality of respiratory signals since different physiological mechanisms cause the respiratory modulations in the ECG and PPG. Therefore, the strengths of individual modulations may differ between the two signals, impacting extracted respiratory signals. The physiological mechanisms have been reported previously in Bailón *et al* (2006a) and Meredith *et al* (2012), and are summarised in table 1

Table 1. Physiological mechanisms causing respiratory modulation of the electrocardiogram (ECG) and photoplethysmogram (PPG). For a comprehensive treatment see Bailón *et al* (2006a) and Meredith *et al* (2012).

Modulation	ECG	PPG
BW	Beat morphology is influenced during respiration by two mechanisms: (i) changes in thoracic impedance, and (ii) changes in the orientation of the electrical axis of the heart relative to ECG electrodes (Bailón *et al* 2006a).	Changes in tissue blood volume caused by: (i) transmitted changes in intrathoracic pressure; and (ii) vasoconstriction of arteries during inhalation, transferring blood to more central veins (Nitzan *et al* 2006)
AM		Stroke volume is reduced during inhalation due to changes in intrathoracic pressure, affecting pulse amplitude (Meredith *et al* 2012)
FM	FM is due to respiratory sinus arrhythmia (RSA) which causes heart rate to increase during inspiration and decrease during exhalation. It is caused by at least three mechanisms: (i) changes in intrathoracic pressure during inhalation stretch the sino-atrial node, increasing heart rate (HR); (ii) increased vagal outflow during exhalation reduces HR; and (iii) reduced intrathoracic pressure during inhalation decreases left ventricular stroke volume, causing a baroreflex-mediated increase in HR (Larsen *et al* 2010)	

(although they are not fully understood). FM-based BR algorithms have previously been found to perform better when using the PPG rather than the ECG (Constant *et al* 1999, Dash *et al* 2010, Karlen *et al* 2011). In contrast, in our previous study of the performance of BR algorithms in young healthy subjects, we observed that algorithms tended to perform better when the ECG was used as an input signal (Charlton *et al* 2016a). Further research is required to determine whether one signal is superior to the other for measurement of respiratory signals.

The sampling frequency of the input signal may affect the quality of respiratory signals. This is most important for the ECG signal since many of the feature-based respiratory signals are calculated from measurements of the QRS-spike, which contains high frequency content. It is intuitively appealing to use high sampling rates to ensure that respiratory modulations are captured as precisely as possible. Indeed, several studies have used high-fidelity equipment sampling the ECG and PPG at up to 1 kHz (Bailón *et al* 2006b, Selvaraj *et al* 2009). However, it is desirable to be able to use low fidelity equipment since it will make ECG- and PPG-based BR estimation more widely accessible, particularly in resource-constrained settings. For instance, smart phones with PPG sampling rates as low as 30 Hz (Nam *et al* 2014) are widely accessible. Previous studies have assessed the effect of sampling frequency on ECG analyses, including the measurement of heart rate and QT interval variability (Merri *et al* 1990, Baumert *et al* 2016). These recommended avoiding the use of lower ECG sampling frequencies such as $\leqslant$200 Hz. Any reduction in respiratory signal quality due to lower sampling frequencies must be appreciated to allow appropriate equipment to be selected for each clinical setting.

2.2. Physiological factors

Age may affect the quality of respiratory signals since some of the physiological mechanisms which cause respiratory modulations of the ECG and PPG diminish with age. In particular, respiratory sinus arrhythmia (RSA, which causes FM) and chest wall expansion (which is linked to BW and

AM) both diminish with age (Moll and Wright 1972, O'Brien *et al* 1986, Pikkujamsa *et al* 1999, Charlton *et al* 2016a). Indeed, FM-based ECG algorithms of BR have been found to perform worse in older subjects (Cysarz *et al* 2008, Schäfer and Kratky 2008, Sobron *et al* 2010, Orphanidou *et al* 2013). However, a previous investigation into the effect of age on BW-based PPG algorithms of BR did not find a difference in performance with age (Nilsson *et al* 2000). Further investigation is required to determine the extent to which each respiratory modulation is affected by age. This is particularly important given that populations worldwide are ageing rapidly (Bloom *et al* 2015).

It has also been suggested that gender may influence the quality of respiratory signals. The amplitude of FM in the PPG has been observed to be greater in women than men (Li *et al* 2010). In contrast, the amplitude of BW in the PPG does not appear to be influenced by gender (Nilsson *et al* 2000). If the qualities of respiratory signals differ between women and men then potentially different respiratory signals could be extracted for each gender.

It has also been reported that the amplitudes of respiratory modulations are affected by a subject's BR. This would be particularly significant if it results in a reduction in the performance of BR algorithms at abnormally low or high BRs, since it is important to be able to detect these extreme values to ensure patient safety (Seymour *et al* 2016). Respiratory sinus arrhythmia (RSA), the mechanism which causes FM, is reduced above a certain corner respiratory frequency (Hirsch and Bishop 1981). Furthermore, it has been observed that AM of the PPG is reduced at increasing BRs (Lázaro *et al* 2014b). It has been suggested that the reduced amplitude of respiratory modulations at elevated BRs causes a reduction in the performance of BR algorithms (Caggiano and Reisman 1996, Johansson and Strömberg 1999, Johnston and Mendelson 2004, Selvaraj *et al* 2009, Nam *et al* 2014). Another study found that FM-based ECG algorithms performed worse at higher BRs, whereas AM-based algorithms performed better at higher BRs (Nemati *et al* 2010). It has been proposed that there is a range of BRs within which BR algorithms perform best, and that performance is reduced for BRs outside of this range. However, the exact range is unclear, having being reported as 8–11 breaths per minute (Johnston and Mendelson 2004), and 16–20 breaths per minute (Orphanidou *et al* 2013).

3. Methods

The methods used for both data collection and signal processing have, in part, already been described in Charlton *et al* (2016a). Those relevant to this study are presented here.

3.1. Technical and physiological factors

The technical and physiological factors investigated in this study are listed in table 2. The investigations were carried out as follows. Firstly, the respective qualities of respiratory signals extracted from finger and ear PPG signals were compared. The measurement site associated with lower quality respiratory signals was eliminated from further analyses. Secondly, respiratory signals extracted from laboratory and clinical signal acquisition equipment were compared. Similarly, the signal acquisition equipment associated with lower quality respiratory signals was eliminated from further analyses. Finally, the influences of the remaining technical factors, and the physiological factors, on respiratory signal quality were assessed.

3.2. Participants

Two groups of healthy adults participated as part of the VORTAL study (National Clinical Trial 01472133): young subjects aged between 18 and 40 years, and elderly subjects aged over 70 years. Ethical approval was obtained from the London Westminster Research Ethics

Table 2. Technical and physiological factors investigated in this study which may influence the quality of respiratory signals extracted from the electrocardiogram (ECG) and photoplethysmogram (PPG).

Technical	Physiological
PPG measurement site: finger or ear	Age
Signal acquisition equipment: laboratory or clinical	Gender
Input signal: ECG or PPG	Breathing rate (BR)
Sampling frequency	

Committee (11/LO/1667). Subjects who had co-morbidities or were receiving medications that might significantly affect the functioning of the cardiac, respiratory and autonomic nervous systems were excluded.

3.3. Signal acquisition

High fidelity laboratory (lab) equipment was used to acquire lead II ECG, finger PPG, ear PPG, and oral-nasal pressure signals. The lab equipment consisted of a 1902 amplifier, a Power 1401 analogue-to-digital converter and Spike2 v.7.09 acquisition software (all Cambridge Electronic Design, Cambridge, UK). Finger and ear PPGs were transduced using MLT1020FC and MLT1060EC infrared reflection plethysmographs respectively (AD Instruments, CO Springs, USA). Oral-nasal pressure was transduced using an Ultima Dual Airflow differential pressure transducer (Braebon Medical Corporation, Kantata, ON, Canada) connected to a P1300 Pro-Flow oral-nasal cannula (Philips Respironics, Murrysville, PA, USA). Signals were sampled at 500 Hz.

In addition, clinical equipment was used to simultaneously acquire Lead II ECG and finger PPG signals. The signals were monitored using an IntelliVue MP30 clinical monitor (Philips Medical Systems, Boeblingen, Germany) and captured using ixTrend acquisition software (v.2.0.0 Express, Ixellence GmbH, Wildau, Germany) at 500 Hz and 125 Hz, respectively.

A 10 min recording was acquired from each subject whilst laid supine, consisting of all signals acquired simultaneously.

ECG and PPG signals were downsampled incrementally from the original sampling frequencies to 50 Hz for the ECG and 8 Hz for the PPG. They were then interpolated at the original sampling frequency using cubic-spline interpolation to assess the impact of sampling frequency.

3.4. Quality assessment

ECG, PPG and oral-nasal pressure signals were segmented into adjacent windows of 32 s duration. The quality of each signal during each window was assessed using the methods described below. Any windows in which any of the required signals were of low quality were excluded from analyses.

ECG and PPG signal quality was assessed using the algorithm described in Orphanidou *et al* (2015). This algorithm assesses signal quality in two stages. Firstly, the timings of heart beats are identified in each signal to check for implausibly extreme beat-to-beat intervals or average heart rates. Windows with implausible values are deemed to be low quality. Secondly, a template beat is constructed, and the correlation between each individual beat and the template is calculated. If the average correlation coefficient for the window is below an empirically

determined threshold (0.66 for the ECG and 0.86 for the PPG) then the window is deemed to be of low quality.

The quality of the oral-nasal pressure signal was assessed by calculating its signal-to-noise ratio using a modified periodogram. Any windows with a low signal-to-noise ratio were deemed to be of low quality, with the threshold for exclusion set to eliminate windows in which breaths could not be identified visually.

3.5. Extraction of respiratory signals

Several techniques have been proposed for extraction of respiratory signals from the ECG and PPG. In this study the techniques listed in table 3, and reported previously in Charlton *et al* (2016a), were used to extract a wide range of respiratory signals.

Filter-based techniques, X_{A1} to X_{A3}, were implemented as described in table 3, followed by elimination of frequency content outside of the range of plausible respiratory frequencies by band-pass filtering.

Feature-based extraction was conducted as follows. Very high frequencies were eliminated using low-pass filters with −3 dB cutoffs of 100 and 35 Hz for the ECG and PPG, respectively. An additional 50 Hz notch filter was used to eliminate mains interference in the ECG. Beat detection was performed on the ECG using a QRS detector based upon the algorithm of Pan, Hamilton and Tompkins (Pan and Tompkins 1985, Hamilton and Tompkins 1986), and on the PPG using the incremental-merge segmentation (IMS) algorithm (Karlen *et al* 2012). R-waves and pulse peaks were detected as the maxima at or between detected beats. QRS troughs were detected as the minima within the 0.10 s prior to R-waves (Ruangsuwana *et al* 2010), and pulse troughs as the minima between pulse peaks (Johansson 2003). One of the beat-by-beat features, X_{B1} to X_{B13}, was obtained as described in table 3. Features derived from ectopic beats were eliminated using the algorithm described in Mateo and Laguna (2003). The beat-by-beat features were generated at a variable rate (the heart rate). The time-series of these features was resampled at 5 Hz using linear interpolation since subsequent processing required a constant sampling frequency (Karlen *et al* 2013). Frequency content outside of the range of plausible respiratory frequencies was eliminated by band-pass filtering.

The plausible range of respiratory frequencies was determined as follows. The lower cutoff was fixed at 4 breaths per minute. The upper limit was set to 36 breaths per minute to bisect the maximum BR and minimum heart rate (HR) in the dataset (33 breaths per minute and 40 beats per minute respectively). This ensured that the extracted respiratory signals were not contaminated with cardiac frequency content.

3.6. Respiratory signal assessment

The quality of extracted respiratory signals was assessed as follows. Signals were segmented into the 32 s windows defined during quality assessment. For each window, the extracted respiratory signals and simultaneous reference respiratory signal were resampled at 5 Hz using linear interpolation, band-pass filtered between 4 and 60 breaths per minute to remove non-respiratory frequencies, and temporally aligned to account for any phase difference between the two signals. The quality of each extracted respiratory signal was calculated as the correlation between that extracted respiratory signal and the reference oral-nasal pressure signal (see figure 1). The correlation was calculated using Pearson's linear correlation coefficient (CC) (Li *et al* 2010). The remainder of the methodology varied according to the particular factor being investigated as follows:

Table 3. Techniques for extraction of respiratory signals. Techniques can be used with the ECG and PPG, except X_{B7} and X_{B8}, which can only be used with the ECG. Adapted from Charlton *et al* (2016a) (CC BY 3.0).

Respiratory signal	Description
	Filter-based, X_{A1} to X_{A4}
X_{A1} (BW)	Band-pass filter between plausible respiratory frequencies (Lindberg *et al* 1992)
X_{A2} (AM)	The maximum amplitude of the continuous wavelet transform (CWT) within plausible cardiac frequencies (30–220 beats per minute) (Addison and Watson 2004)
X_{A3} (FM)	The frequency corresponding to the maximum amplitude of the CWT within plausible cardiac frequencies (Addison and Watson 2004)
	Feature-based, X_{B1} to X_{B9}
X_{B1} (BW)	Mean amplitude of troughs and proceeding peaks (Charlton *et al* 2016a)
X_{B2} (AM)	Difference between the amplitudes of troughs and proceeding peaks (Karlen *et al* 2013)
X_{B3} (FM)	Time interval between consecutive peaks (Orphanidou *et al* 2013, Karlen *et al* 2013)
X_{B4} (BW)	Mean signal value between consecutive troughs (Ruangsuwana *et al* 2010)
X_{B5} (BW, AM)	Peak amplitude (Karlen *et al* 2013)
X_{B6} (BW, AM)	Trough amplitude (Ruangsuwana *et al* 2010)
X_{B7} (FM)	QRS duration (Rajkumar and Ramya 2013). Q and S waves were identified as the minima immediately before and after the R wave (Ruangsuwana *et al* 2010)
X_{B8} (AM, FM)	QRS area (Sobron *et al* 2010), defined as the integral of the ECG between Q and S waves after subtraction of a baseline linearly interpolated between Q and S waves
X_{B9} (BW)	Kernel principal component analysis using a radial basis function, with the variance of the Gaussian kernel determined by maximising the difference between the first eigenvalue and sum of the remainder (Widjaja *et al* 2012)
X_{B10} (FM)	PPG pulse width estimated using a wave boundary detection algorithm (Lázaro *et al* 2013)
X_{B11} (AM, FM)	QR slopes measured by fitting a straight line to an 8 ms interval of ECG centred on the time of maximum upslope between Q- and R-waves (Lázaro *et al* 2014a)
X_{B12} (AM, FM)	RS slopes measured by fitting a straight line to an 8 ms interval of ECG centred on the time of maximum downslope between R- and S-waves (Lázaro *et al* 2014a)
X_{B13} (AM, FM)	QRS-wave angles measured as the difference between QR and RS slopes (Lázaro *et al* 2014a)

- Comparisons between subjects (e.g. young versus elderly subjects) were performed using subject-specific CCs. The subject-specific CC was found for each subject and for each respiratory signal by calculating the median of the extracted respiratory signal's CCs from each of a particular subject's windows.
- Comparisons between input signals (e.g. ear versus finger PPG) were performed using subject-specific differences in CCs. The subject-specific difference in CCs was found for each subject and for each respiratory signal by calculating the median difference between the CCs for the extracted respiratory signal when extracted from a first input signal, and the CCs for the extracted respiratory signal when extracted from a second input signal.

3.7. Statistical analysis

Statistical tests were performed using a significance level of $\alpha = 0.05$. The Wilcoxon signed rank test was used to compare simultaneously recorded signals, such as ear and finger PPGs. The Wilcoxon rank sum test was used for results from independent groups, such as those acquired from young and elderly subjects. When testing for trends, such as across a range of reference BRs, the Mann-Kendall monotonic trend test was used, as described in Hamed

(2008). Kendall's rank CC was reported for statistically significant trends as an indicator of the strength of the trend, as described in Kendall (1938). The directionality of statistically significant differences was determined by using a normal approximation to compute a z-statistic corresponding to an approximate p-value, the polarity of which indicated directionality.

During the analysis of each factor, a statistical test was performed to identify any changes in the quality of each respiratory signal. Since 12 signals were tested for the ECG, and 10 for the PPG, this would usually increase the probability of a type I error (false rejection of a null hypothesis) considerably. Therefore, a Holm-Sidak correction was made to ensure that the probability of a type I error was fixed at 5% (Sidak 1967, Holm 1979).

Respiratory signals extracted from the ECG and PPG were ranked by identifying the signal with the greatest median CC (control), and assessing the probability that each other signal's CCs originated from the same distribution as the control signal.

4. Results

4.1. Recruitment and data characteristics

Data were acquired from 44 young subjects (aged 18–39), and 16 elderly subjects (aged over 70) meeting the trial entry criteria. Three young subjects were excluded since their recordings were incomplete. Therefore, data from a total of 57 subjects' (41 young and 16 elderly) were analysed. The demographic characteristics of the analysed subjects are provided in table 4. Data from each subject contained a median (lq – uq) of 20 (19 – 20) 32 s windows. The number of high quality windows for each signal are given in table 5. The ranges of BR and HR in the dataset were 4–33 breaths per minute and 40–100 beats per minute, respectively.

4.2. PPG measurement site

The results of the comparisons between finger and ear PPG signals are shown in table 6. Seven out of eleven respiratory signals had significantly greater CCs when extracted from finger PPG signals than ear PPG signals.

4.3. Signal acquisition equipment

The results of the comparisons between signals acquired from laboratory and clinical equipment are shown in table 7. The respiratory signals extracted from laboratory and clinical signals were mostly comparable, with the quality of a minority of signals differing significantly in favour of one set of recording equipment. Since neither set of recording equipment provided consistently higher CCs, only clinical signals were considered in the remaining comparisons to increase the clinical applicability of the conclusions.

4.4. Input signal: ECG or PPG

The subject-specific CCs of each respiratory signal extracted from the ECG and PPG are shown in figure 3. All respiratory signals were ranked more highly when extracted from the ECG than the PPG. Indeed, all of the PPG-extracted respiratory signals had significantly lower CCs than ECG(X_{B2}), the ECG-extracted respiratory signal with the greatest median CC. Despite this, ECG and PPG signals were retained in the remainder of the analysis. This ensured the results were applicable to situations where device design considerations or clinical conditions enforce the use of one particular signal for practical, rather than performance-based, reasons.

Table 4. Demographic characteristics.

Characteristic	Young cohort	Elderly cohort
No. subjects	41	16
Age, med (lq – uq) (years)	29 (26 – 31)	75 (72 – 78)
BMI, med (lq – uq) (kg m^{-2})	23 (21 – 26)	25 (24 – 26)
Female (%)	51	56

Table 5. Data characteristics.

Characteristic	No. high quality 32 s windows per subject, med (lq – uq)
Reference respiratory signal (ref)	19 (18 – 20)
Laboratory ECG and ref	19 (18 – 20)
Laboratory finger PPG and ref	18 (16 – 20)
Laboratory ear PPG and ref	19 (17 – 20)
Clinical ECG and ref	19 (18 – 20)
Clinical finger PPG and ref	19 (17 – 20)

Table 6. Comparison of finger and ear PPG measurement sites: subject-specific differences in correlation coefficients (CCs) of respiratory signals extracted from finger (fin) and ear PPG signals are expressed as median (lower – upper quartiles) Fin—Ear PPG CCs.

Respiratory signal	Subject-specific differences in CCs	
X_{A1} (BW)	0.06 (−0.01 – 0.17)	Fin[a]
X_{A2} (AM)	−0.01 (−0.09 – 0.05)	
X_{A3} (FM)	0.00 (−0.01 – 0.01)	
X_{B1} (BW)	0.07 (0.01 – 0.19)	Fin[a]
X_{B2} (AM)	0.03 (−0.03 – 0.14)	
X_{B3} (FM)	0.11 (0.04 – 0.18)	Fin[a]
X_{B4} (BW)	0.06 (0.00 – 0.14)	Fin[a]
X_{B5} (BW, AM)	0.08 (−0.01 – 0.16)	Fin[a]
X_{B6} (BW, AM)	0.08 (0.00 – 0.18)	Fin[a]
X_{B9} (BW)	0.02 (−0.03 – 0.09)	
X_{B10} (FM)	0.05 (−0.05 – 0.16)	Fin[a]

[a]Respiratory signals with significantly greater CCs.

4.5. Sampling frequency

Figure 4 shows the CCs of respiratory signals extracted from ECG and PPG signals at different sampling frequencies. Filter-based respiratory signals (X_{A1} to X_{A3}) were largely unaffected by sampling frequency. The CCs of all feature-based respiratory signals (X_{B1} to X_{B13}) extracted from the ECG except one were significantly lower at reduced sampling frequencies, beginning below 250 Hz. In contrast, CCs of feature-based respiratory signals extracted from the PPG were not reduced until the sampling frequency was below 16 Hz.

Table 7. Comparison of laboratory and clinical equipment: subject-specific differences in correlation coefficients (CCs) of respiratory signals extracted from clinical (clin) and laboratory (lab) equipment are expressed as median (lower − upper quartiles).

	Subject-specific differences in CCs			
Respiratory signal	ECG		PPG	
X_{A1} (BW)	0.01 (−0.05 − 0.10)		0.05 (−0.02 − 0.15)	Clin[a]
X_{A2} (AM)	0.01 (−0.01 − 0.05)	Clin[a]	−0.02 (−0.07 − 0.03)	
X_{A3} (FM)	0.00 (0.00 − 0.01)		−0.01 (−0.04 − 0.00)	Lab[a]
X_{B1} (BW)	0.04 (−0.01 − 0.13)	Clin[a]	0.07 (−0.01 − 0.15)	Clin[a]
X_{B2} (AM)	0.01 (−0.02 − 0.10)		−0.09 (−0.16 − 0.01)	Lab[a]
X_{B3} (FM)	0.00 (0.00 − 0.00)		0.02 (−0.01 − 0.07)	Clin[a]
X_{B4} (BW)	0.02 (−0.03 − 0.11)		0.02 (−0.05 − 0.10)	
X_{B5} (BW, AM)	0.04 (0.00 − 0.11)	Clin[a]	0.01 (−0.08 − 0.12)	
X_{B6} (BW, AM)	0.03 (−0.04 − 0.10)		0.14 (0.04 − 0.20)	Clin[a]
X_{B7} (FM)	0.00 (−0.06 − 0.05)		NA	
X_{B8} (AM, FM)	0.01 (−0.06 − 0.08)		NA	
X_{B9} (BW)	0.01 (−0.03 − 0.09)		0.04 (−0.06 − 0.13)	
X_{B10} (FM)	NA		−0.04 (−0.12 − 0.06)	
X_{B11} (AM, FM)	0.01 (−0.08 − 0.04)		NA	
X_{B12} (AM, FM)	0.02 (−0.06 − 0.12)		NA	
X_{B13} (AM, FM)	0.02 (−0.07 − 0.06)		NA	

[a]Respiratory signals with significantly greater CCs.

4.6. Age

The results of comparisons between young and elderly subjects are shown in table 8. The CCs of PPG(X_{B3}), a respiratory signal based on FM, were significantly lower in elderly subjects than young subjects. The CCs of other respiratory signals based on FM, namely PPG(X_{A3}), ECG(X_{A3}) and ECG(X_{B3}), were also substantially lower in elderly subjects, although these differences ($p = 0.04$, $p = 0.09$ and $p = 0.01$ respectively) did not reach statistical significance, partly due to the correction for multiple comparisons. For comparison, when the equivalent analysis was performed on laboratory signals, only the CCs of PPG(X_{B3}) and PPG(X_{B10}), both FM-based respiratory signals, were significantly lower in elderly subjects.

4.7. Gender

A similar sub-group analysis of male and female subjects was performed. No significant differences in quality were found for any respiratory signals between male and female subjects.

4.8. Breathing rate

The results of comparisons of respiratory signals at different reference BRs are shown in figure 5. The CCs of most respiratory signals extracted from the ECG, and all extracted from the PPG decreased significantly with increasing BR.

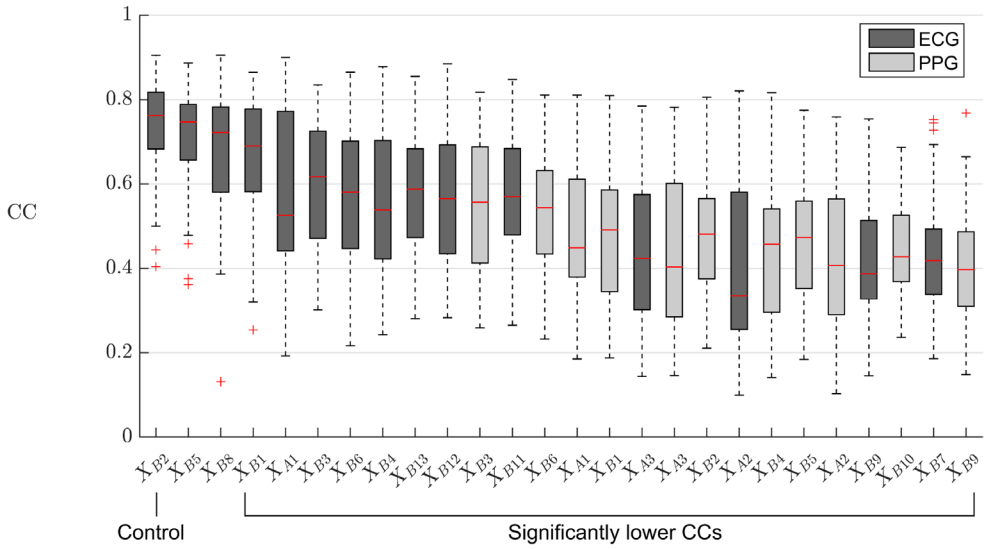

Figure 3. Comparison of respiratory signals extracted from the ECG and PPG: correlation coefficients (CCs) for each respiratory signal extracted from the ECG and PPG. The respiratory signal with the greatest median CC, ECG(X_{B2}), was used as a control against which each respiratory signal was compared in turn. Those with significantly lower CCs than this control are indicated. Note that all of the signals extracted from the PPG had significantly lower CCs than the best ECG-extracted signal. Outliers are shown by +.

5. Discussion

A plethora of algorithms have been proposed for estimation of BR from the ECG and PPG by extracting a respiratory signal. In this study we investigated the effects of a range of technical and physiological factors on the quality of respiratory signals. The main conclusions are listed in table 9, and are now considered in turn.

5.1. PPG measurement site

In current clinical practice the PPG is routinely measured at either the finger or ear for determining pulse rate and arterial blood oxygen saturation. Whilst cardiac modulation of the PPG remains strong across a range of anatomical sites, the respiratory modulation is affected by probe position (Nilsson *et al* 2007). Our finding, that many of the respiratory signals extracted from the finger PPG were of higher quality than those from the ear PPG, informs our recommendation that the finger PPG should be used in preference to the ear PPG for BR estimation. This was the case for most of the respiratory signals based on solely BW or FM: PPG(X_{A1}), PPG(X_{B1}), PPG(X_{B4}), PPG(X_{B3}) and PPG(X_{B10}). However, we did not find significant differences in the qualities of respiratory signals based on AM: PPG(X_{A2}) and PPG(X_{B2}). This is in direct contrast to previous work, where BW was found to be stronger at the ear than the finger (Shelley *et al* 2006, Nilsson *et al* 2007). Despite using the same transducers as in Shelley *et al* (2006), the finger PPG tended to have a greater signal-to-noise ratio than the ear PPG in our recordings. This may explain the observed differences between our findings and previous findings, although we are unable to determine whether the cause of the lower signal-to-noise ratio at the ear was physiological or technical.

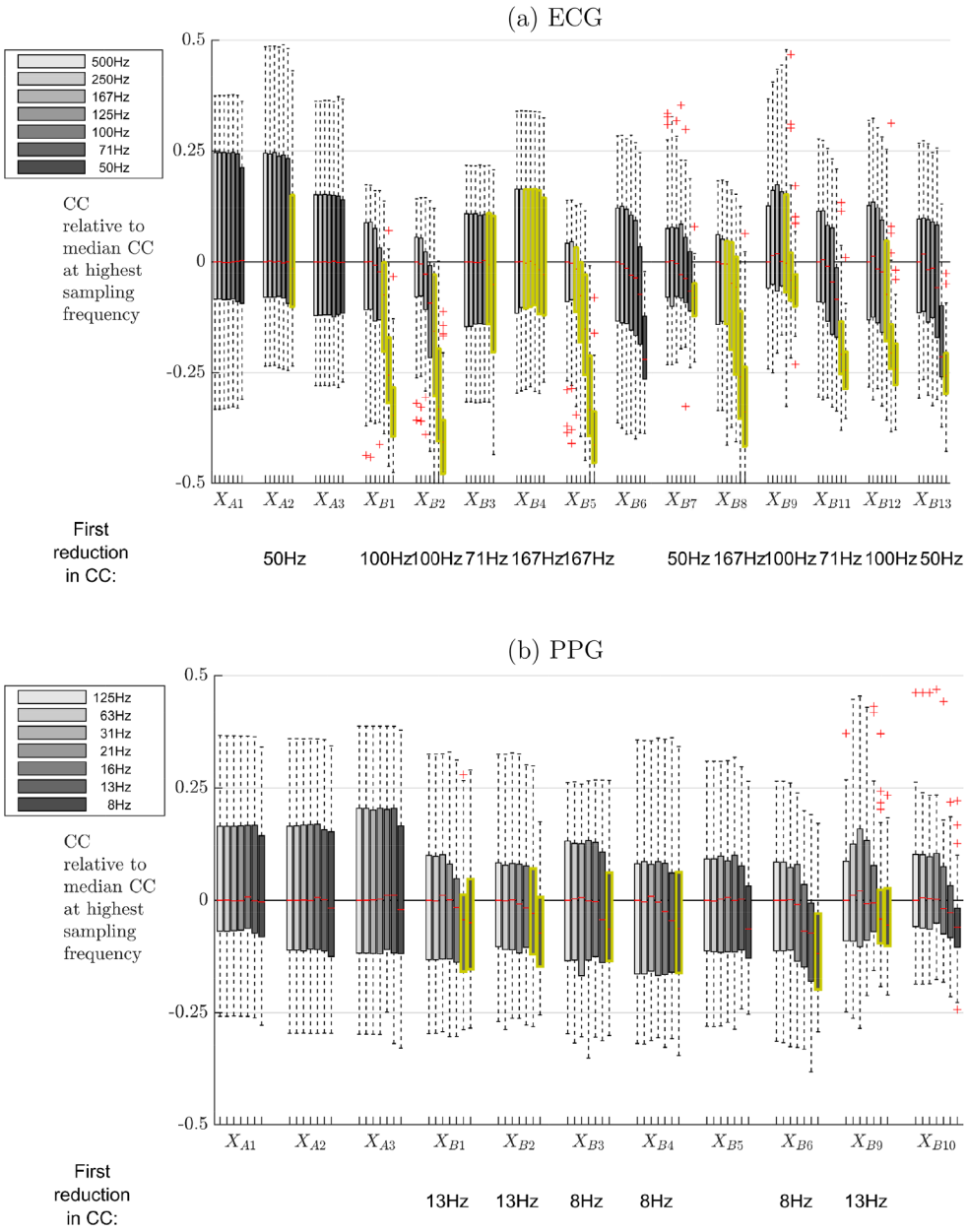

Figure 4. Comparison of sampling frequencies: subject-specific correlation coefficients (CCs) are shown for each respiratory signal extracted from the ECG and PPG at different sampling frequencies. Significant reductions in CCs at lower sampling frequencies are highlighted in yellow. Filter-based respiratory signals (X_{A1} to X_{A3}) were largely unaffected by sampling frequency, whereas the CCs of many feature-based respiratory signals (X_{B1} to X_{B13}) were significantly reduced at lower sampling frequencies. Significant reductions in CCs of ECG-extracted respiratory signals occurred at sampling frequencies below 250 Hz, whereas reductions in CCs of PPG-extracted respiratory signals occurred below 16 Hz. (a) ECG. (b) PPG.

Table 8. Comparison of young and elderly subjects: subject-specific correlation coefficients (CCs) for young and elderly subjects, expressed as median (lower − upper quartiles).

	Subject-specific CCs		
Respiratory signal	Young	Elderly	
ECG(X_{A1})	0.52 (0.44 − 0.76)	0.60 (0.42 − 0.80)	
ECG(X_{A2})	0.32 (0.23 − 0.58)	0.37 (0.30 − 0.53)	
ECG(X_{A3})	0.43 (0.34 − 0.60)	0.31 (0.25 − 0.47)	
ECG(X_{B1})	0.66 (0.57 − 0.77)	0.72 (0.64 − 0.79)	
ECG(X_{B2})	0.76 (0.68 − 0.82)	0.77 (0.68 − 0.81)	
ECG(X_{B3})	0.66 (0.52 − 0.75)	0.44 (0.35 − 0.63)	
ECG(X_{B4})	0.52 (0.42 − 0.68)	0.56 (0.43 − 0.82)	
ECG(X_{B5})	0.74 (0.64 − 0.79)	0.76 (0.69 − 0.78)	
ECG(X_{B6})	0.59 (0.48 − 0.69)	0.50 (0.41 − 0.80)	
ECG(X_{B7})	0.42 (0.36 − 0.51)	0.41 (0.30 − 0.44)	
ECG(X_{B8})	0.73 (0.61 − 0.79)	0.66 (0.44 − 0.76)	
ECG(X_{B9})	0.40 (0.34 − 0.56)	0.36 (0.31 − 0.45)	
ECG(X_{B11})	0.57 (0.48 − 0.64)	0.56 (0.48 − 0.74)	
ECG(X_{B12})	0.55 (0.43 − 0.68)	0.59 (0.51 − 0.70)	
ECG(X_{B13})	0.56 (0.47 − 0.68)	0.65 (0.56 − 0.70)	
PPG(X_{A1})	0.44 (0.38 − 0.57)	0.51 (0.34 − 0.65)	
PPG(X_{A2})	0.41 (0.29 − 0.57)	0.37 (0.27 − 0.53)	
PPG(X_{A3})	0.44 (0.33 − 0.61)	0.30 (0.25 − 0.40)	
PPG(X_{B1})	0.48 (0.35 − 0.56)	0.49 (0.36 − 0.63)	
PPG(X_{B2})	0.48 (0.39 − 0.57)	0.47 (0.35 − 0.57)	
PPG(X_{B3})	0.64 (0.50 − 0.73)	0.38 (0.32 − 0.55)	Young > Elderly[a]
PPG(X_{B4})	0.45 (0.30 − 0.54)	0.48 (0.28 − 0.55)	
PPG(X_{B5})	0.46 (0.35 − 0.54)	0.51 (0.34 − 0.58)	
PPG(X_{B6})	0.55 (0.44 − 0.61)	0.54 (0.41 − 0.63)	
PPG(X_{B9})	0.41 (0.33 − 0.48)	0.32 (0.28 − 0.52)	
PPG(X_{B10})	0.44 (0.37 − 0.53)	0.41 (0.34 − 0.50)	

[a] Respiratory signals with significantly different CCs.

5.2. Signal acquisition equipment

In this study the qualities of respiratory signals measured using laboratory and clinical equipment were compared to determine whether there were differences which prevented the use of clinical monitoring signals for BR estimation. Counter-intuitively, more respiratory signals were of higher quality when measured using clinical equipment than when using laboratory equipment. This suggests that BR algorithms could be applied to this particular clinical monitor without a loss in performance. This is in keeping with previously reported results (Charlton *et al* 2014). However, this conclusion cannot be extrapolated to other clinical monitors which may contain different filtering procedures. Therefore, the potential effects of signal filtering performed by commercial devices warrant further investigation.

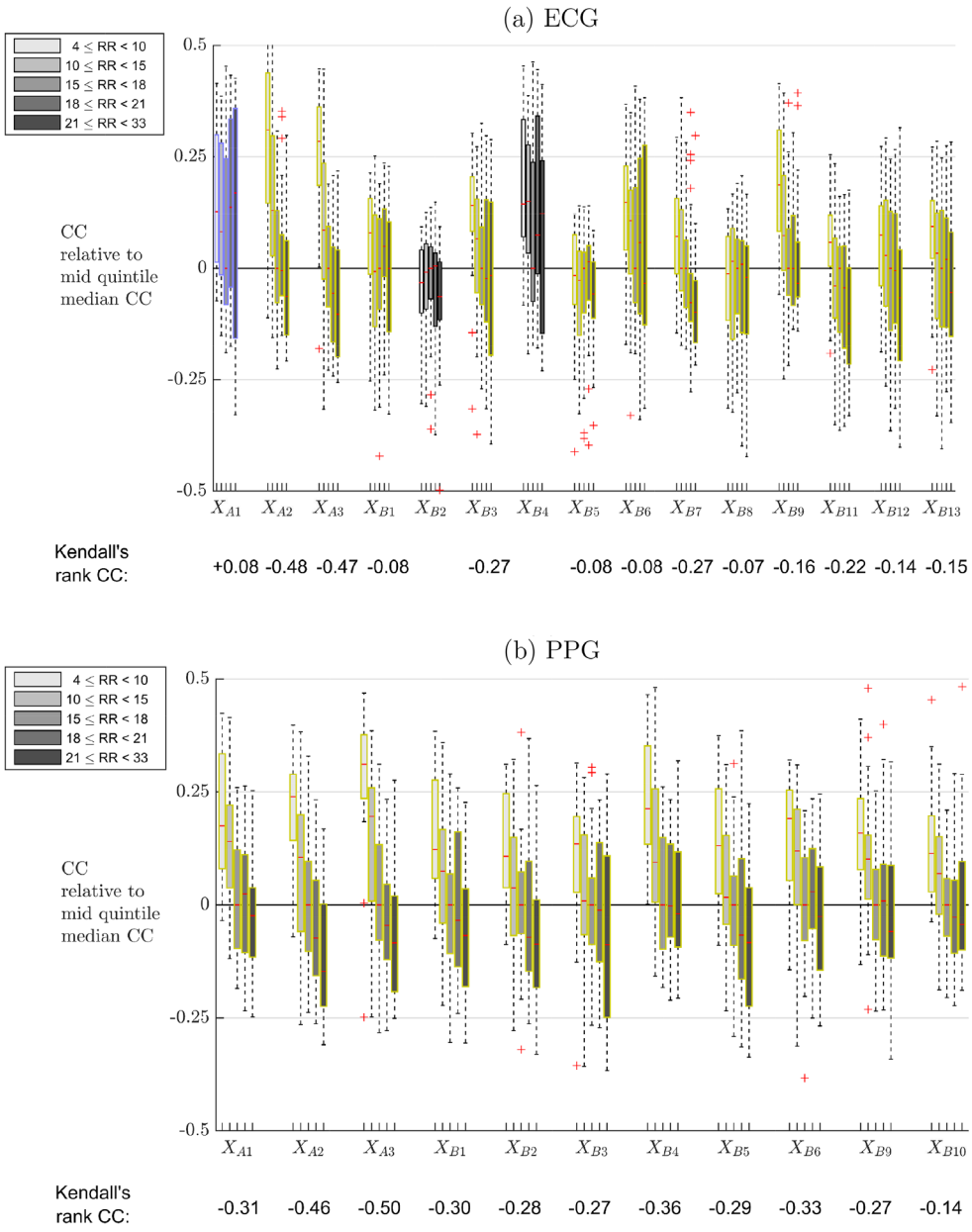

Figure 5. Trends in correlation coefficients (CCs) with breathing rate (BR, measured in breaths per minute): the subject-specific CCs of respiratory signals obtained at different BRs are shown for (a) ECG, and (b) PPG. Significant trends indicating reduced CCs at increased BRs are highlighted in yellow, with blue indicating trends where CCs increased at increased BRs.

5.3. Input signal: ECG or PPG

The vast majority of respiratory signals were ranked more highly when extracted from the ECG compared to the PPG. Therefore, we recommend that where there is a choice of signals, the ECG should be preferred to the PPG. However, when taking individual measurements

Table 9. Main conclusions on the technical and physiological factors affecting respiratory signals extracted from the ECG and PPG.

Factor	Conclusion
Technical factors	
PPG measurement site	We recommend using the finger rather than the ear PPG for measuring respiratory signals
Signal acquisition equipment	We did not find evidence to suggest that high fidelity laboratory equipment provided superior measurement of ECG- and PPG-extracted respiratory signals when compared to a clinical monitor
Input signal: ECG or PPG	We recommend using the ECG rather than the PPG for measuring respiratory signals where possible
Sampling frequency	We recommend using sampling frequencies of $\geqslant$250 Hz for the ECG, and $\geqslant$16 Hz for the PPG, for measuring respiratory signals
Physiological factors	
Age	We recommend avoiding the use of FM-based respiratory signals when estimating BR in elderly subjects
Gender	There were no differences in the qualities of respiratory signals between women and men
BR	We recommend caution when using BR algorithms in settings where the detection of elevated BRs is required since the qualities of most respiratory signals were reduced at higher BRs. However, further investigations are required to confirm this finding

the PPG is often more convenient to acquire since a PPG finger probe can be more quickly attached than ECG electrodes. In contrast, our results suggest that no trade-off is required between convenience and performance when performing continuous monitoring using wearable sensors, since in this setting ECG electrodes have been found to be better tolerated than a PPG probe (Bonnici *et al* 2014).

5.4. Sampling frequency

We hypothesised that the use of higher sampling frequencies would result in higher quality respiratory signals. In the ECG, this effect continued up to 250 Hz, above which there was no significant benefit to using higher sampling frequencies. This finding supports the use of BR algorithms with current clinical monitors since wearable sensors and static monitors typically sample the ECG at up to 256 Hz (Bonnici *et al* 2012) and 500 Hz (this study). It is in line with previous work which recommended avoiding the use of ECG sampling frequencies of $\leqslant$200 Hz for heart rate variability analyses (Baumert *et al* 2016). In the PPG, significant reductions in quality were only apparent below 16 Hz. This is promising since it suggests that non-specialist equipment, such as smart phones (Lázaro *et al* 2015), tablets (Nam *et al* 2014), and non-contact video cameras (Tarassenko *et al* 2014) should not be hindered by their relatively low sampling frequencies when measuring respiratory signals.

5.5. Age

We observed that one FM-based respiratory signal was of significantly lower quality in elderly subjects compared to young subjects, and others exhibited non-significant trends towards lower quality in elderly subjects. This is in keeping with previous work, and informs our recommendation that FM-based respiratory signals should be avoided when using BR algorithms

with elderly subjects. Previously, BR algorithms which fuse estimates from different respiratory signals have commonly included FM-based signals to increase precision (Karlen *et al* 2013, Orphanidou *et al* 2013). Further research is required to determine whether the performance of these fusion algorithms could be improved in elderly subjects by exchanging the FM-based input for an alternative respiratory signal. Further investigation is also required to determine whether the quality of FM-based respiratory signals is similarly reduced in diseases associated with reduced autonomic nervous system functionality.

5.6. Gender

The lack of differences between male and female subjects in this study indicates that gender is not an important factor in determining the quality of respiratory signals. This is supported by the relatively high number of subjects in each subgroup (30 female and 27 male), suggesting that the lack of differences was not simply due to a lack of statistical power. Indeed, the present sample size is greater than in a previous analysis of differences due to gender (14 female and 14 male) (Li *et al* 2010).

5.7. Breathing rate

In this study most respiratory signals were of lower quality at higher BRs, in keeping with previous work. This suggests that the performance of BR algorithms may be gradually reduced as the true BR increases. This would be clinically significant since an elevated BR is a key marker of clinical deterioration (Seymour *et al* 2016). If this translates into an unacceptable performance of BR algorithms at elevated BRs then this would severely limit their clinical utility.

A potential concern with this analysis of the effect of BR on respiratory signal quality is that the observed reduction in quality is due to inter-subject differences in quality. For instance, a latent subgroup of subjects with lower respiratory signal quality may also breathe at higher BRs by coincidence, rather than there being a causal link between elevated BR and reduced quality.

5.8. Limitations

The key limitations to this study are as follows. Firstly, this study was conducted in a laboratory setting with healthy subjects. This allowed us to isolate the influences of technical factors, age and gender, without common confounders such as the reduction in autonomic nervous system functionality associated with diabetes. Further investigation is required prior to applying the findings to clinical settings. Secondly, we used a particular set of laboratory equipment, and a particular clinical monitor. Therefore, the findings regarding signal acquisition equipment may not be universally applicable to all manufacturers' equipment. Thirdly, a known statistical property of correcting for multiple comparisons is that the probability of a type II error is increased. Consequently, some smaller differences in signal qualities may not have been identified. Finally, only single-lead ECG signals were considered in this study. Multi-lead signals may provide higher quality respiratory signals for two reasons. Firstly, different leads may provide the highest quality respiratory signals in different subjects due to thorax anisotropy and intersubject electrical axis variability (Bailón *et al* 2006a). Secondly, additional techniques are available for extracting respiratory signals from multi-lead signals including: extracting the electrical axis direction; and compensating for noisy beats in individual leads whilst still extracting a respiratory signal (Bailón *et al* 2006b).

6. Conclusion

In this study we assessed the impact of technical and physiological factors on the extraction of respiratory signals from the ECG and PPG. This was achieved through analysis of ECG, PPG and reference respiratory signals from young and elderly healthy subjects. The main technical recommendations for extraction of high quality respiratory signals were: (i) to measure the PPG at the finger rather than the ear; (ii) where possible, to use the ECG rather than the PPG; and, (iii) to use sampling frequencies of $\geqslant$250 Hz for the ECG, and $\geqslant$16 Hz for the PPG. The main clinical recommendations were: (i) to avoid the use of FM-based respiratory signals in elderly subjects; and, (ii) to expect the qualities of respiratory signals to be reduced at higher BRs. These recommendations will be helpful to equipment manufacturers to inform the design of monitoring devices, and to clinicians for determining whether BR algorithms should be used in their particular setting.

Future work should investigate whether these findings are consistent across other datasets. In addition, further work is required to determine whether additional factors encountered in clinical practice affect the qualities of extracted respiratory signals, such as ectopic beats and pathological cardiovascular and respiratory changes.

The dataset, respiratory signal extraction algorithms, and analysis code used in this study are publicly available at http://peterhcharlton.github.io/RRest. These resources allow future researchers to reproduce the analyses presented here, and to use the dataset for additional studies.

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Data access statement

The data and code used in this research are openly available at http://peterhcharlton.github.io/RRest. Further information about the data and conditions of access can be found by emailing *research.data@kcl.ac.uk*.

References

Addison P and Watson J 2004 Secondary transform decoupling of shifted nonstationary signal modulation components: application to photoplethysmography *Int. J. Wavelets Multiresolution Inf. Process.* **2** 43–57

Alastruey J, Khir A W, Matthys K S, Segers P, Sherwin S J, Verdonck P R, Parker K and Peiró J 2011 Pulse wave propagation in a model human arterial network: assessment of 1D visco-elastic simulations against *in vitro* measurements *J. Biomech.* **44** 2250–8

Bailón R, Sornmo L and Laguna P 2006a ECG-derived respiratory frequency estimation *Advanced Methods and Tools for ECG Data Analysis* ed G D Clifford *et al* (London: Artech House Publishers) ch 8, pp 215–44

Bailón R, Sörnmo L and Laguna P 2006b A robust method for ECG-based estimation of the respiratory frequency during stress testing *IEEE Trans. Biomed. Eng.* **53** 1273–85

Baumert M, Schmidt M, Zaunseder S and Porta A 2016 Effects of ECG sampling rate on QT interval variability measurement *Biomed. Signal Process. Control* **25** 159–64

Bloom D E, Chatterji S, Kowal P, Lloyd-Sherlock P, McKee M, Rechel B, Rosenberg L and Smith J P 2015 Macroeconomic implications of population ageing and selected policy responses *Lancet* **385** 649–57

Bonnici T, Charlton P, Clifton D, Alastruey J, Tarassenko L, Watkinson P and Beale R 2014 Continuous physiological monitoring of ambulatory patients *MEC Annual Meeting and Bioengineering14 Programme and Abstracts* p 38

Bonnici T, Orphanidou C, Vallance D, Darrell A and Tarassenko L 2012 Testing of wearable monitors in a real-world hospital environment: What lessons can be learnt? *Conf. Proc. 9th Wearable and Implantable BSNs* pp 79–84

Caggiano D and Reisman S 1996 Respiration derived from the electrocardiogram: a quantitative comparison of three different methods *Conf. Proc. IEEE 22nd Annual Northeast Bioengineering* pp 103–4

Charlton P, Bonnici T, Clifton D, Alastruey J, Tarassenko L, Beale R and Watkinson P 2014 The influence of recording equipment on the accuracy of respiratory rate estimation from the electrocardiogram and photoplethysmogram *MEC Annual Meeting and Bioengineering14 Programme and Abstracts* p 96

Charlton P H, Bonnici T, Tarassenko L, Clifton D A, Beale R and Watkinson P J 2016a An assessment of algorithms to estimate respiratory rate from the electrocardiogram and photoplethysmogram *Physiol. Meas.* **37** 610–26

Charlton P H, Villarroel M and Salguiero F 2016b Waveform analysis to estimate respiratory rate *Secondary Analysis of Electronic Health Records* ed MIT Critical Data (Berlin: Springer) ch 26, pp 377–90

Constant I, Laude D, Murat I and Elghozi J L 1999 Pulse rate variability is not a surrogate for heart rate variability *Clin. Sci.* **97** 391–7

Cretikos M A, Bellomo R, Hillman K, Chen J, Finfer S and Flabouris A 2008 Respiratory rate: the neglected vital sign *Med. J. Aust.* **188** 657–9

Cysarz D, Zerm R, Bettermann H, Frühwirth M, Moser M and Kröz M 2008 Comparison of respiratory rates derived from heart rate variability, ECG amplitude, and nasal/oral airflow *Ann. Biomed. Eng.* **36** 2085–94

Dash S, Shelley K H, Silverman D G and Chon K H 2010 Estimation of respiratory rate from ECG, photoplethysmogram, and piezoelectric pulse transducer signals: a comparative study of time-frequency methods *IEEE Trans. Biomed. Eng.* **57** 1099–107

Elgendi M 2012 On the analysis of fingertip photoplethysmogram signals *Curr. Cardiol. Rev.* **8** 14–25

Feldman J M 2006 Can clinical monitors be used as scientific instruments? *Anesthesia Analgesia* **103** 1071–2

Hamed K H 2008 Trend detection in hydrologic data: the Mann–Kendall trend test under the scaling hypothesis *J. Hydrol.* **349** 350–63

Hamilton P S and Tompkins W J 1986 Quantitative investigation of QRS detection rules using the MIT/BIH arrhythmia database *IEEE Trans. Biomed. Eng.* **33** 1157–65

Hirsch J and Bishop B 1981 Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate *Am. J. Physiol.* **241** H620–9

Høiseth L Ø, Hoff I E, Hagen O A, Kirkebøen K A and Landsverk S A 2015 Respiratory variations in the photoplethysmographic waveform amplitude depend on type of pulse oximetry device *J. Clin. Monit. Comput.* **30** 317–25

Holm S 1979 A simple sequentially rejective multiple test procedure *Scand. J. Stat.* **6** 65–70

Johansson A 2003 Neural network for photoplethysmographic respiratory rate monitoring *Med. Biol. Eng. Comput.* **41** 242–8

Johansson A and Strömberg P A 1999 Estimation of respiratory volumes from the photoplethysmographic signal. Part 2: A model study *Med. Biol. Eng. Comput.* **37** 48–53

Johnston W S and Mendelson Y 2004 Extracting breathing rate information from a wearable reflectance pulse oximeter sensor *Conf. Proc. IEEE Engineering in Medicine and Biology Society* pp 5388–91

Karlen W, Ansermino J M and Dumont G 2012 Adaptive pulse segmentation and artifact detection in photoplethysmography for mobile applications *Conf. Proc. IEEE Engineering in Medicine and Biology Society* pp 3131–4

Karlen W, Brouse C J, Cooke E, Ansermino J M and Dumont G 2011 Respiratory rate estimation using respiratory sinus arrhythmia from photoplethysmography *Conf. Proc. IEEE Engineering in Medicine and Biology Society* pp 1201–4
Karlen W, Raman S, Ansermino J M and Dumont G a 2013 Multiparameter respiratory rate estimation from the photoplethysmogram *IEEE Trans. Biomed. Eng.* **60** 1946–53
Kendall M G 1938 A new measure of rank correlation *Biometrika* **30** 81–93
Larsen P D, Tzeng Y C, Sin P Y W and Galletly D C 2010 Respiratory sinus arrhythmia in conscious humans during spontaneous respiration *Respiratory Physiol. Neurobiol.* **174** 111–8
Lázaro J, Alcaine A, Romero D, Gil E, Laguna P, Pueyo E and Bailón R 2014a Electrocardiogram derived respiratory rate from QRS slopes and R-wave angle *Ann. Biomed. Eng.* **42** 2072–83
Lázaro J, Bailón R, Laguna P, Nam Y, Chon K and Gil E 2014b Respiratory rate influence in the resulting magnitude of pulse photoplethysmogram derived respiration signals *Conf. Proc. CinC* pp 289–92
Lázaro J, Gil E, Bailón R, Mincholé A and Laguna P 2013 Deriving respiration from photoplethysmographic pulse width *Med. Biol. Eng. Comput.* **51** 233–42
Lázaro J, Nam Y, Gil E, Laguna P, Bailón R and Chon K 2015 Respiratory rate derived from smartphone-camera-acquired pulse photoplethysmographic signals *Physiol. Meas.* **36** 2317–33
Li J, Jin J, Chen X, Sun W and Guo P 2010 Comparison of respiratory-induced variations in photoplethysmographic signals *Physiol. Meas.* **31** 415–25
Lindberg L G, Ugnell H and Öberg Å P 1992 Monitoring of respiratory and heart rates using a fibre-optic sensor *Med. Biol. Eng. Comput.* **30** 533–7
Lovett P B, Buchwald J M, Stürmann K and Bijur P 2005 The vexatious vital: neither clinical measurements by nurses nor an electronic monitor provides accurate measurements of respiratory rate in triage *Ann. Emergency Med.* **45** 68–76
Mateo J and Laguna P 2003 Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal *IEEE Trans. Biomed. Eng.* **50** 334–43
Meredith D J, Clifton D, Charlton P, Brooks J, Pugh C W and Tarassenko L 2012 Photoplethysmographic derivation of respiratory rate: a review of relevant physiology *J. Med. Eng. Technol.* **36** 1–7
Merri M, Farden D C, Mottley J G and Titlebaum E L 1990 Sampling frequency of the electrocardiogram for spectral analysis of the heart rate variability *IEEE Trans. Biomed. Eng.* **37** 99–106
Moll J M and Wright V 1972 An objective clinical study of chest expansion *Ann. Rheumatic Dis.* **31** 1–8
Nam Y, Lee J and Chon K H 2014 Respiratory rate estimation from the built-in cameras of smartphones and tablets *Ann. Biomed. Eng.* **42** 885–98
Nemati S, Malhotra A and Clifford G D 2010 Data fusion for improved respiration rate estimation *EURASIP J. Adv. Signal Process.* **2010** 926305
Nilsson L, Goscinski T, Kalman S, Lindberg L G and Johansson A 2007 Combined photoplethysmographic monitoring of respiration rate and pulse: a comparison between different measurement sites in spontaneously breathing subjects *Acta Anaesthesiologica Scand.* **51** 1250–7
Nilsson L, Johansson A and Kalman S 2000 Monitoring of respiratory rate in postoperative care using a new photoplethysmographic technique *J. Clin. Monit. Comput.* **2000** 309–15
Nitzan M, Faib I and Friedman H 2006 Respiration-induced changes in tissue blood volume distal to occluded artery, measured by photoplethysmography *J. Biomed. Opt.* **11** 040506
O'Brien I, O'Hare P and Corrall R 1986 Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function *Br. Heart J.* **57** 109–10
Orphanidou C, Bonnici T, Charlton P, Clifton D, Vallance D and Tarassenko L 2015 Signal-quality indices for the electrocardiogram and photoplethysmogram: derivation and applications to wireless monitoring *IEEE J. Biomed. Health Inform.* **19** 832–8
Orphanidou C, Fleming S, Shah S and Tarassenko L 2013 Data fusion for estimating respiratory rate from a single-lead ECG *Biomed. Signal Process. Control* **8** 98–105
Pan J and Tompkins W J 1985 A real-time QRS detection algorithm *IEEE Trans. Biomed. Eng.* **32** 230–6
Pikkujamsa S M, Makikallio T H and Sourander L B 1999 Cardiac interbeat interval dynamics from childhood to senescence *Circulation* **100** 393–9
Pimentel M A F, Charlton P H and Clifton D A 2015 Probabilistic estimation of respiratory rate from wearable sensors *Wearable Electronics Sensors* vol 15, ed S C Mukhopadhyay (Berlin: Springer) pp 241–62
Rajkumar K and Ramya K 2013 Respiration rate diagnosis using single lead ECG in real time *Global J. Med. Res.* **13** 7–11
Ruangsuwana R, Velikic G and Bocko M 2010 Methods to extract respiration information from ECG signals *Conf. Proc. ICASSP* pp 570–3

Schäfer A and Kratky K W 2008 Estimation of breathing rate from respiratory sinus arrhythmia: comparison of various methods *Ann. Biomed. Eng.* **36** 476–85

Selvaraj N, Jaryal A K, Santhosh J, Deepak K K and Anand S 2009 Influence of respiratory rate on the variability of blood volume pulse characteristics *J. Med. Eng. Technol.* **33** 370–5

Seymour C W *et al* 2016 Assessment of clinical criteria for sepsis *JAMA* **315** 762–74

Shelley K H 2007 Photoplethysmography: beyond the calculation of arterial oxygen saturation and heart rate *Anesthesia Analgesia* **105** S31–6

Shelley K H, Jablonka D H, Stout R G, Silverman D G, Awad A A and Rezkanna H 2006 What is the best site for measuring the effect of ventilation on the pulse oximeter waveform? *Anesthesia Analgesia* **103** 372–7

Sidak Z 1967 Rectangular confidence regions for the means of multivariate normal distributions *J. Am. Stat. Assoc.* **62** 626–33

Sobron A, Romero I and Lopetegi T 2010 Evaluation of methods for estimation of respiratory frequency from the ECG *Conf. Proc. CinC* vol 45 pp 513–6

Tarassenko L, Villarroel M, Guazzi A, Jorge J, Clifton D A and Pugh C 2014 Non-contact video-based vital sign monitoring using ambient light and auto-regressive models *Physiol. Meas.* **35** 807–31

Widjaja D, Varon C, Dorado A C, Suykens J a K and Van Huffel S 2012 Application of kernel principal component analysis for single-lead-ECG-derived respiration *IEEE Trans. Biomed. Eng.* **59** 1169–76